

EDITOR'S PAGE



A Delayed Answer to the Calcium Blocker Question

WILLIAM W. PARMLEY, MD, FACC

Editor-in-Chief

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Since its presentation as an abstract in March 1995 (1) and its subsequent publication in August 1995 (2), the case-control study by Psaty et al. has generated controversy. Their results suggested that short-acting calcium channel blocking agents increased the rate of myocardial infarction in patients treated for hypertension. However, case-control studies cannot address this issue because of potential unrecognized bias; at best they are useful in generating a hypothesis (3). The potential for misleading results is suggested by a recent case-control study that indicated that beta-adrenergic blocking agents increase the rate of sudden death in patients treated for hypertension (4).

The controversy was fueled by the report of Furberg et al. (5), which reported the results of a meta-analysis of prospective, randomized, placebo-controlled trials of short-acting nifedipine in patients with myocardial infarction and unstable angina. The results suggested that doses >60 mg/day increased mortality. Although criticized for a number of reasons (6,7), the data, together with other studies, suggest that short-acting calcium channel blockers should not be used in postmyocardial infarction patients. The controversy regarding calcium channel blockers now seems to be debated at every major cardiology and hypertension meeting. Frequently, the debates are more theatrical than scientific. This has polarized opinion and in some cases led to severe undue criticism of the participants (8).

The following represent some of my thoughts regarding the controversy:

1. Case-control studies in hypertension cannot address the issue. Nevertheless, one should be cautious about using short-acting calcium channel blockers.
2. Long-acting calcium channel blockers are effective in treating hypertension and do not cause the cyclic pattern of hypotension and the reflex increase in catecholamine levels that, for example, short-acting nifedipine causes. One gets

some reassurance regarding long-acting amlodipine from the PRAISE trial (9) and the neutral effect of felodipine in V-HEFT 3 (10). I personally am comfortable in using all long-acting calcium channel blockers in patients with hypertension. They are also very effective in vasospastic angina and exercise-induced angina.

Table 1. Newer Trials of Calcium Channel Blockers

Study/Agent	Hypothesis	Projected No. of Patients	Primary End Points	Comment
NORDIL Nifedipine (Pfizer/Bayer AG)	Compares nifedipine with conventional therapy to prevent events	12,000	CV mortality and morbidity, including MI and stroke	A probe design, randomized trial in 480 centers in Norway and Sweden, with an average of 5 yr of treatment
PREDICT Diltiazem (Hoechst-Marion-Roussel)	Assess high risk population vs. chlorthalidone	6,000–7,000	Mortality, CV events (fatal and nonfatal)	3-yr follow-up; enrollment of mild to moderate hypertension at high risk in 300 centers
CONVINCE Verapamil using a new formulation, COER Covera-HS (Searle)	Verapamil vs. thiazide or beta-blocker	15,000	MI, stroke, death	Randomized, prospective 4–6-yr follow-up; targeting morning events by matching drug effect to natural circadian rhythm

CONVINCE = Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (Principal Investigator, Henry Black, Rush Presbyterian St. Lukes Hospital, Chicago, Illinois); CV = cardiovascular; MI = myocardial infarction; NORDIL = Nordic Diltiazem Study (Principal Investigator, Lennart Hansson, Uppsala, Sweden); PREDICT = Prospective Randomized Evaluation of Diltiazem CD Trial (Principal Investigator, William Applegate, University of Tennessee, Memphis).

Address for correspondence: William W. Parmley, MD, Editor-in-Chief, *Journal of the American College of Cardiology*, 415 Judah Street, San Francisco, California 94122.

3. The long-term safety and efficacy of calcium channel blockers can only be addressed by long-term prospective trials, and such trials are under way. In addition to the five hypertension trials (HOT, STOP, ALLHAT, INSIGHT, EURO-SYST) and three heart failure trials (V-HEFT III, PRAISE-2, MACH-1) listed in the editorial by Salim Yusuf (11), there are three newer trials of calcium channel blockers (Table 1). Thus, the answer will be delayed; but I personally do not believe that the use of all calcium channel blockers should be avoided, as some have suggested. I do agree, however, that short-acting calcium channel blockers are best avoided. Hopefully, the intensity of the controversy will diminish as the results of prospective, randomized trials become available.

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